Alzheimer's and Related Diseases Research Award Fund

2016-2017 ALZHEIMER'S RESEARCH AWARD FUND RECIPIENTS ANNOUNCED

The Alzheimer's and Related Diseases Research Award Fund (ARDRAF) was established by the Virginia General Assembly in 1982 to stimulate innovative investigations into Alzheimer's disease and related disorders along a variety of avenues, such as the causes, epidemiology, diagnosis, and treatment of the disorder; public policy and the financing of care, and the social and psychological impacts of the disease upon the individual, family, and community. The awards this year have been enhanced by a $25,000 donation from Mrs. Russell Sullivan of Fredericksburg, in memory of her husband who died of dementia. Sullivan awards are indicated by an asterisk (*). The ARDRAF competition is administered by the Virginia Center on Aging in the School of Allied Health Professions at Virginia Commonwealth University. Questions about the projects may be directed to the investigators or the ARDRAF administrator, Dr. Constance Coogle (ccoogle@vcu.edu).

UVA   Matthew J. Barrett, MD, MSc, Jason Druzgal, MD, PhD, and Scott Sperling, PsyD
         Nucleus Basalis of Meynert Degeneration in Parkinson Disease Cognition

Dementia in Parkinson disease (PD) is a major source of morbidity. Degeneration of neurons in the nucleus basalis of Meynert contributes to dementia in PD. For this reason the nucleus basalis of Meynert has been identified as a potential intervention point to treat dementia in PD, and deep brain stimulation has been proposed as a potential therapy. As a preliminary step toward testing this procedure in PD, the investigators will determine whether Magnetic Resonance Imaging measures of nucleus basalis of Meynert volume correlate with cognition in PD. This is critically important to identify PD patients that would likely benefit from an intervention. They will also investigate whether specific genetic factors are associated with reduced nucleus basalis of Meynert volume in PD. Determining factors associated with nucleus of basalis Meynert degeneration would allow treatment to be targeted to more vulnerable PD patients. This research will provide important information for the future study of deep brain stimulation of the nucleus basalis of Meynert to treat dementia in PD.*(Dr. Barrett may be contacted at 434/243-2012, mjb5t@virginia.edu; Dr. Druzgal may be contacted at 434/982-1736, tjd4m@virginia.edu; Dr. Sperling may be contacted at 434/982-1012, sas7yr@virginia.edu)*

VCU   Jennifer Inker, MBA, MS, Tracey Gendron, PhD, and J. James Cotter, PhD*
         Use of Antipsychotic Medications by Residents with Dementia in Assisted Living Facilities

This research will deliver Virginia's first comprehensive effort to: 1) establish a baseline rate of antipsychotic medication use in residents with dementia in Virginia's assisted living facilities (ALFs); 2) explore what ALF characteristics correlate with the use of antipsychotic medications; and 3) investigate reasons why antipsychotic medications are used in ALF residents with dementia. With the expertise and guidance of an interdisciplinary, interagency research advisory committee, VCU will use a use a mixed methods approach with two phases. Phase one will employ a self-administered survey of licensed ALFs in Virginia to identify facility characteristics (rural/urban, chain/independent, staffing, etc.), followed by aggregate data on the rate of administration to ALF residents with dementia of the four most widely used antipsychotic medications. Phase two, which will be informed by the findings of phase one, will include three case studies of ALFs, with one each from below, at, and above the median rate of antipsychotic medication use as determined in the quantitative phase. The findings of this critical research will be used to inform policy and practice. *(Ms. Inker may be contacted at 804/828-1565, inkerjl@vcu.edu; Dr. Gendron may be contacted at 804/828-1565, tlgendro@vcu.edu; Dr. Cotter may be contacted at 804/828-1565, jcotter@vcu.edu)*

College of William and Mary   Oliver Kerscher, PhD and Munira Basrai, PhD*

STUbL-dependent clearance of transcriptionally-active, aggregate-prone proteins from the nucleus

Patients suffering from Huntington's disease experience a wide-range of degenerative symptoms from short-term memory loss to motor function. On the cellular level, the patient's brain atrophies due to the accumulation of a toxic huntingtin protein that, at least in part, disrupts the transcriptional program of specific neurons. The investigators determined that human RNF4, an enzyme involved in targeted protein degradation, prevents the abnormal transcriptional activity associated with a mutant, aggregation-prone fragment of huntingtin. This study aims to identify and study the proteins that counteract the transcriptional aberrations that plague neuronal cells affected by huntingtin and other aggregation-prone proteins. The research will also determine whether RNF4 reduces the transcriptional activity of mutant huntingtin protein in a tissue culture model of Huntington's disease, and establish the role that RNF4 plays in stripping transcriptionally-active huntingtin on a genome-wide scale.

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VCU   Rory McQuiston, PhD*

AAV-Induced Tau Pathophysiology in Interneurons of the Mouse Hippocampus

Tau proteins are important for normal brain cell molecular trafficking, but when pathological tau begins to misfold and aggregate, the result is dysfunctional synaptic signaling and eventual cell death. One of the first regions of the brain to display tau pathology in Alzheimer's disease (AD) is the entorhinal cortex (EC). EC neurons innervate the hippocampus, but little is known about how early tau pathology affects specific types of hippocampal inhibitory neurons or how it disturbs the synaptic connections between these regions. This study will employ a mouse model that has a highly aggressive form of the human tau protein to investigate how tau affects these cells using state-of-the art physiological and immunochemical techniques. Greater understanding of changes in inhibitory neuron function may lead to novel therapies to treat early Alzheimer's disease and other neurodegenerative disorders.

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UVA   Andrés Norambuena, PhD*

Amyloid Beta Peptides, Nutrient Signaling and Mitochondria Dysfunction: An Unholy Triad in Alzheimer's Disease

Normal mitochondrial functions allow the proper delivery of nutrient-derived energy in the form of ATP, providing timely clearance of reactive oxygen species and buffering of calcium. These functions are fundamental for maintaining proper synaptic activity, but how neurons coordinate nutrient signaling with mitochondrial activity and how its dysregulation promotes AD needs to be investigated further. Oligomeric forms of the amyloid-ß peptide (AßOs) initiate signaling pathways leading to loss of dendritic function, changes in mitochondrial dynamics, insulin signaling disruption, and cell death. While these studies have provided valuable information about the molecular players involved in AD pathogenesis, the molecular mechanisms involved are poorly understood. The investigator has developed a two-photon fluorescence lifetime imaging assay which allows for the detection of changes in mitochondrial activity in live cortical neurons in culture. The results mechanistically link insulin resistance to mitochondrial dysfunction and AD. This new funded study is intended to move basic findings closer to being translated into clinical applications by using a newly developed human-derived neural cell model grown on three dimensional cultures.

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VA Tech   **Jyoti S. Savla, PhD, Karen A. Roberto, PhD, and Rosemary Blieszner, PhD***
    Families in Rural Appalachia Caring for Older Relatives with Dementia

The purpose of this research is to increase understanding of how families in rural Appalachia manage care for older relatives with Alzheimer's disease or other dementias. The primary aim is to learn about their approaches to caregiving and uncover patterns of current use of community services as well as their views of formal service use in the future. The research is based on a guiding model of caregiving stress and influences on service use, and incorporates multiple pieces of information about both individual and community factors that affect care needs and service use. The study employs multiple strategies to gather information. Ten family caregivers will be invited to participate in an in-depth in-person interview to provide insight about their caregiving situation, and their needs and difficulties in receiving informal and formal help services. Guided by the themes and patterns of these interviews, 60 family caregivers will respond to an in-depth telephone survey followed by brief calls about daily events for 7 days. This combination of using open-ended questions and then asking specific questions to a larger group of participants is very effective for generalizing and validating the qualitative findings. The findings from this project will reveal the diverse approaches to caregiving for persons with Alzheimer's disease living in Appalachian Virginia.
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Christopher   **Lisa S. Webb, PhD and Darlene A. Mitrano, PhD**
Newport   ***Comparative Biochemical and Behavioral Analysis of the 3xTg-AD Mouse Model of***
University   ***Alzheimer's Disease***
The investigators will use bioanalytical techniques and behavioral measures to characterize blood lipid profiles and olfactory abilities in the triple transgenic mouse model of Alzheimer's disease (3xTg-AD). They will test the mice at three month intervals over the course of a year and compare results from the 3xTg-AD mice to age- and sex-matched mice without AD to pinpoint when blood lipid profiles are altered and when the declines in olfactory abilities become statistically different. The results of this study will better define the biochemical and behavioral phenotype of the 3xTg-AD mice, an important model used to illuminate how AD develops in humans. *(Dr. Webb may be contacted at 757/594-7056, lwebb@cnu.edu; Dr. Mitrano may be contacted at 757/594-8093, darlene.mitrano@cnu.edu)*
2016-2017 ARDRAF Awards Committee